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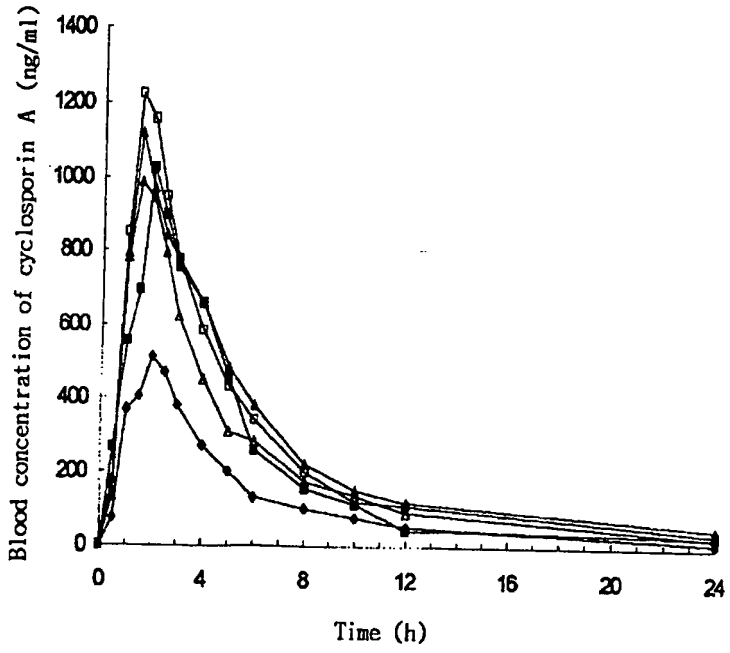
(54) Title: CYCLOSPORIN-CONTAINING MICROEMULSION PRECONCENTRATE COMPOSITION

(57) Abstract

The present invention relates to a microemulsion preconcentrate composition comprising (1) cyclosporin as an active component; (2) alkyl ester of polycarboxylic acid and/or carboxylic acid ester of polyols as a lipophilic solvent; (3) oil; and (4) surfactant. The composition according to the present invention is characterized in that it dissolves in an external phase such as water, artificial gastric fluid and artificial intestinal fluid by controlling the mixing ratio of the components thereby to get the microemulsion form of inner phase diameter of 100 nm or below. The composition according to the present invention can be formulated as the dosage form of a soft capsule, a hard capsule sealed with a gelatin banding at the conjugated portion, or an oral liquid preparation for oral administration. Especially, in the case that the composition according to the present invention is formulated in a soft capsule, the resultant capsule does not show the disadvantages of the prior arts such as the reactivity of hydrophilic solvent with gelatin shell of soft capsule and the volatility of hydrophilic solvent. It is because the existing patents use a hydrophilic solvent as an essential component of their compositions but the present invention does not use any hydrophilic solvent.



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CYCLOSPORIN-CONTAINING MICROEMULSION PRECONCENTRATE COMPOSITION

TECHNICAL FIELD

The present invention is related to a microemulsion preconcentrate composition comprising a cyclosporin as an active component; an alkyl ester of polycarboxylic acid and/or a carboxylic acid ester of polyols as a lipophilic solvent; an oil; and a surfactant.

BACKGROUND ART

Cyclosporin is a high molecular peptide compound consisting of 11 amino acids which achieves its potent immunosuppressive activity by inhibiting the growth and differentiation of T cells. There are many cyclosporins such as cyclosporin A, B, C, D, G, etc. depending on the structure of constituent amino acids, but cyclosporin A is preferably used in the clinical field since its pharmacological activity and clinical indication and effectiveness are well established in the art. Cyclosporin was found in *Tolypocladium inflatum* gams by Borel *et al.* in 1976, and developed as antibiotics at first. After it was found during the safety test that cyclosporin inhibits the growth of lymphocytes, cyclosporin has become the focus of the world's attention as the only immunosuppressant which can specifically affect only lymphocytes, and made the technical development in the organ transplantation possible.

Cyclosporin has a unique structure, which is a cyclic oligopeptide consisting of 11 amino acids. The seven amino acids of cyclosporin are N-methylated. The four remaining protonated nitrogen atoms can form intermolecular hydrogen bonds with carbonyl groups, which contribute

substantially to the rigidity of the cyclosporin skeleton. Therefore, it has a remarkably hydrophobic property, and is relatively insoluble in water (for cyclosporin A, 0.04 mg/ml at 25°C). Due to such a low water-solubility of cyclosporin A, the bioavailability of cyclosporin A is known as be 30% or less. It was reported that the absorption of such an insoluble compound is greatly influenced by bile juice secretions, the amount of fat in food, etc. In case of cyclosporin A, it has been reported that differences in absorption between individuals are as great as about 5~50 %. When cyclosporin is administered for a long time, it shows renal toxicity, liver toxicity, etc. The renal side effects comprise a reduction of glomerular filtration, an increase in proximal renal tubular reabsorption and chronic progressive deterioration of nephron.

Cyclosporin has a large dosage unit and a narrow therapeutic index as well as the said properties, and the condition of patient to be treated with cyclosporin is generally unstable. Therefore, it is very difficult to establish an optimum drug dosage regimen for survival of transplanted patient through maintenance of efficient and constant blood concentration that can prohibit side effects and rejection. Numerous studies have been conducted to overcome the said properties and to develop an improved pharmaceutical formulation. Such studies have been mainly concentrated on the means that are used to solubilize cyclosporin. Typical examples include not only mixed solvent systems consisting of vegetable oil and surfactant, but also microspheres, the formations of powdery composition using adsorption, inclusion complexes, solid dispersions, and other numerous formulations. An oral preparation containing cyclosporin as the primary active ingredient has been commercialized in a solution form and a soft capsule formulation. The preparation uses a mixed vehicle consisting

of vegetable oil, surfactant and solvent to solubilize cyclosporin, but did not overcome the cyclosporin properties, that is, low bioavailability of cyclosporin and large individual difference thereof. Therefore, the preparation has many problems in the clinical use.

Microemulsions were first reported by J. H. Schulman in 1943 and have, since then, been mainly studied for application of cosmetics and as carrier of insoluble drugs. A microemulsion comprises two or more immiscible liquid materials together with surfactant like emulsion, but is a thermally stable and optically transparent unlike emulsion. And the microemulsion has very low surface tension and small particle size of less than 100 nm, which together result in high absorption and permeation properties of drug delivered by microemulsion. The microemulsion is, especially, very useful in solubilization and absorption improvement of insoluble drugs. However, since formation of a microemulsion requires a lot of surfactant, severe mucosal irritation is caused by the microemulsion preparation, and the volume of dosage becomes large. In medical field, microemulsions have thus been utilized only for preparations that are applied to the skin such as preparations for hair, detergents, etc.

In case of cyclosporin as the relative insoluble drug, U. S. Patent No. 4,388,307 discloses an oral liquid preparation, which includes oil, surfactant, and ethanol as the hydrophilic solvent. This preparation is a microemulsion preconcentrate and, therefore, must be diluted with water before it is administered orally. That makes the patient compliance bad, and makes the control of the exact dosage difficult. Since it is also uncomfortable to carry, it is impossible to actually administer to a patient who must undergo cyclosporin therapy for the remaining period of his life.

In order to remove the said disadvantages of liquid preparations, a

microemulsion preconcentrate formulated in the form of soft capsule has been developed. The microemulsion preconcentrate, until now, has comprised drug, hydrophilic solvent, surfactant and oil with appropriate mixing ratio, and could form the microemulsion spontaneously through dissolving in the outer phase such as water and intestinal fluid. However, the hydrophilic solvent used as essential component of microemulsion preconcentrate permeates the gelatin shell of the capsule not only to volatilize, but also to soften the gelatin shell. Those induced the instability of the soft capsules.

In case of the cyclosporin soft capsule containing ethanol as a hydrophilic component, this capsule preparation must contain a large amount of ethanol to solubilize the cyclosporin. However, since ethanol permeates the gelatin shell of the capsule to volatilize even at normal temperature, the content of ethanol is reduced in the course of time. As a result, when the capsules are stored at low temperatures or at normal temperatures for long period, the crystallization of cyclosporin may be caused. The composition change results in a great variation of cyclosporin bioavailability and, therefore, it is impossible to obtain a desired therapeutic effect reliably and reproducibly. As an effort to prevent the volatilization of ethanol from the soft capsule preparations during storage, the soft capsules are enclosed in a special packaging material, such as aluminum blister packaging. However, the problem of great variation of cyclosporin bioavailability is still remained in spite of using the said special packaging since it is impossible to completely prevent the change of ethanol content in the course of time. Using the said special packaging might contribute to an increase of the manufacturing cost and medicinal fee.

To improve the said disadvantages of the use of ethanol as hydrophilic cosurfactant, methods using non-ethanol component as hydrophilic cosurfactant have also been proposed. U. S. Patent No. 5,342,625 discloses the soft capsule preparation formulated with microemulsion concentrate which solves the said problems. This patent discloses a pharmaceutical composition in the form of microemulsion concentrate in which a pharmaceutically acceptable C_{1-5} alkyl or tetrahydrofurfuryl di- or partial- ether of a low molecular mono- or poly-oxy-alkanediol, for example, diethyleneglycol monoethyl ether (e.g. Transcutol), tetrahydrofurfurylalcohol polyethylene glycol ether (e.g. Glycofurol), 1,2-propylene glycol are used as a hydrophilic solvent, and ethanol is used as a hydrophilic co-solvent. However, all the hydrophilic solvents used in this patent are glycols having the alcoholic group (-OH) in their structure. Since such glycols containing -OH group are very hygroscopic, they absorb moisture present in atmosphere and further have a high permeability to gelatin shell. It is, therefore, very difficult to formulate a composition containing such a glycolic cosurfactant into a soft capsule preparation. In encapsulating and first drying steps at the time of preparing soft capsules, particularly, water that is present in the capsule shell is absorbed into the capsule content by the amount corresponding to 20% of the hygroscopic solvent to cause the change in constitutional ratio of the composition. And then, in drying step of those, water is distributed again into the gelatin shell and volatilized from inside of capsule to outside of that through the capsule shell. The composition materials of capsule content migrate also to capsule shell along with water. Therefore, the constitutional ratio of the composition according to this patent is greatly changed, and the change of the preparation appearance from the said

phenomena makes the capsule production yield decreased.

The said hydrophilic solvents used in the formulation disclosed by the above U. S. patent have, furthermore, the softening effect for the gelatin shell of capsule, and induce the pharmaceutical problem that the appearance stability of gelatin capsule is greatly reduced. This problem becomes even more serious when a plasticizer for gelatin, for example, propylene glycol, glycerin, etc. is used as a hydrophilic solvent. The use of propylene glycol as the main solvent is, therefore, limited highly. Propylene glycol can be used generally in approximately 5% or less of capsule contents, and may be used in approximately 10% or less together with a hardening agent for gelatin shell at the most. The appearance stability of the gelatin shell is greatly reduced when propylene glycol is used in the amount of exceeding the said limits as the content of soft capsule.

Korean Patent Application No. 94-13945 discloses a cyclosporin-containing composition to be formulated in soft capsule (trade name: Neoplanta®) that uses dimethylisosorbide as the hydrophilic cosurfactant for mitigating such disadvantages. This patent describes that the soft capsule preparation using dimethylisosorbide does not show the appearance change of the soft capsule and the content change of the ingredients since dimethylisosorbide has substantially no permeability to the gelatin shell in comparison to the other hydrophilic cosurfactants used in the prior art.

Dimethylisosorbide, which is marketed under the trade name Arlasolve®, i.e., 1,4:3,6-dianhydro-2,5-dimethyl-D-glucitol, is a solvent that has been generally used as a percutaneous absorption enhancer only for topical pharmaceutical ointments or cosmetics such as lotions.

As mentioned above, a conventional microemulsion requires more quantity of surfactant than a general emulsion does. Therefore, in case of a drug that is continuously administered to the patient during his whole life after organ transplantation, for example, cyclosporin, the toxicity of solvent and surfactant contained in the preparation of the microemulsion by long term administration must be also considered. In this connection, the LD_{50} value of dimethylisosorbide is 5.63 ml/kg (rat, per oral). The LD_{50} (rat, per oral) value of the organic solvent of which the toxicity has been relatively well known, is as follows: Acetonitrile, 3.8 g/kg; acetone, 10.7 ml/kg; benzene, 3.8 ml/kg; toluene, 7.53 g/kg; isopropanol, 5.8 g/kg; and butanol, 4.36 g/kg. It is expected that the long-term oral administration of the composition containing dimethylisosorbide may cause problems. Furthermore, the pharmaceutical problems were not improved highly by the use of dimethylisosorbide, since dimethylisosorbide still has the properties, the reactivity with gelatin shell of soft capsule and the volatility and shows the limit as hydrophilic solvent.

U. S. Patent No. 5,583,105 discloses the oral multiple emulsion comprising cyclosporin in which ethanol and tocopheryl polyethylene glycol 1000 succinate, that is a surfactant, are used as essential vehicle, and in which oils or alkyl esters of polycarboxylic acid are used as lipophilic or amphiphilic solvent. This patent describes that alkyl esters of polycarboxylic acid can be used selectively instead of oil, and this patent, in particular, employed acetyl triethyl citrate for formulation of cyclosporin. However, ethanol, which is a hydrophilic and volatile solvent, was also used essentially to constitute the cyclosporin formulation. As mentioned above, the cyclosporin preparations using ethanol for the solubilization of cyclosporin show the problem of pharmaceutical stability,

such as ethanol volatilization through the gelatin shell of capsule, during the storage. Tocopheryl polyethylene glycol 1000 succinate, which was used as a surfactant in this patent, is a product from esterification of tocopheryl acid succinate with polyethylene glycol, and liberates tocopherol after being absorbed into the body. This patent discloses that free tocopherol can reduce the renal toxicity. However, it has not been verified yet, and there could be a drug interaction between cyclosporin and free tocopherol, which may be absorbed in the body exceeding the usual dose depending on the amount of the composition administered, for a long therapy. Moreover, it has been known generally that the lipid-soluble vitamins, such as tocopherol, induce the adverse side effect by accumulation in the body.

As mentioned above, the microemulsion preconcentrates according to prior arts comprise hydrophilic solvent, oil and surfactant as essential and primary composition. In case of formulation of those microemulsion preconcentrates as soft capsule, it has been known generally that hydrophilic solvent reacts with gelatin shell of soft capsule thereby to soften the shell, and volatilizes through the gelatin shell, and that the said phenomena induce the serious problem of preparation stability. There was a try to improve the those disadvantage using dimethylisosorbide as new hydrophilic solvent, but this material has the limit as a primary vehicle because of toxicity thereof and still has the disadvantage of hydrophilic solvent.

The present inventors have studied to develop the cyclosporin-containing composition that could compensate for the disadvantages involved in the various pharmaceutical preparations of the prior art and be

suitable for the formulation into the soft capsule. The present inventors developed the new cyclosporin-containing microemulsion preconcentrate, which comprises lipophilic solvent, surfactant and oil, using lipophilic solvent instead of hydrophilic solvent, which causes in disadvantage of pharmaceutical stability. It was identified that the microemulsion preconcentrate using lipophilic solvent instead of hydrophilic solvent can overcome the various problems of prior arts and thus the present invention was completed.

DESCLOSURE OF INVENTION

The present invention relates to a cyclosporin-containing microemulsion preconcentrate composition that comprises (1) cyclosporin as an active ingredient; (2) alkyl ester of polycarboxylic acid and/or carboxylic acid ester of polyols as a lipophilic solvent; (3) oil; and (4) surfactant.

The first essential component of the cyclosporin-containing microemulsion preconcentrate composition according to the present invention is cyclosporin as an active ingredient. Cyclosporin A is preferred.

The second essential component of the composition according to the present invention is a lipophilic solvent. The lipophilic solvent, which is used in the composition according to the present invention to overcome the disadvantage of hydrophilic solvent, is at least one member selected from alkyl esters of polycarboxylic acid.

The alkyl esters of polycarboxylic acid that can be used in the composition according to the present invention are products from esterification of polycarboxylic acids having carboxylic groups of 2~10, preferably of 3~5, with C_1~C_{10} alcohols.

The carboxylic acid esters of polyols that can be used in the composition according to the present invention are the products from esterification of polyols having hydroxyl groups of 2~10, preferably of 3~5, with C_2~C_{11} carboxylic acids.

The said alkyl esters of polycarboxylic acid and the said carboxylic acid ester of polyols which may be used as lipophilic solvent in the composition according to the present invention, are odorless and colorless oils in liquid state. And their boiling point is higher than 250°C. They does not volatilize at the condition of high temperature during the procedure for soft capsule preparation as well as in the storage state of room temperature, and therefore, they can insure the stability of preparation comprising them. Moreover, the said lipophilic solvent does not show such severe hygroscopic property as glycols show, does not dissolve the gelatin shell, and does not induce the compositional change due to non-volatile and non-permeable for gelatin shell. The said alkyl esters of polycarboxylic acid and or carboxylic acid ester of polyols are lipophilic solvent, which can be applied to the solubilization of insoluble drug such as cyclosporin, and do not induce the problem of preparation stability at the time of preparation and storage of the product.

The alkyl esters of polycarboxylic acid that can be used preferably in the composition according to the present invention comprise triethyl citrate, tributyl citrate, acetyltributyl citrate, acetyltriethyl citrate, etc. The carboxylic acid esters of polyols that can be used preferably in the composition according to the present invention comprise triacetin, etc. They may be used alone or in the mixture of two kinds or more. When the mixture is used, mixing ratio is not particularly limited.

In the cyclosporin-containing microemulsion preconcentrate

composition according to the present invention, the ratio of the lipophilic solvent to cyclosporin is preferably in the range of 1:0.1~5, more preferably 1:1~3 by weight.

The cyclosporin-containing microemulsion preconcentrate composition using lipophilic solvent according to the present invention does not show the pharmaceutical disadvantage, which may be induced by hydrophilic solvent, an essential component in composition of the prior art. In an additional remark, the use of the said lipophilic solvent can not provide only sufficient solubilization effect for cyclosporin but also many advantages, because the said lipophilic solvent does not react with gelatin shell of soft capsule and is not volatile. That is, the said lipophilic solvent neither changes the capsule's appearance, nor causes precipitation of the active ingredient cyclosporin. Moreover, it reduce the cost of manufacturing to provide an economical effect, and it does not even show any problem of solvent toxicity in the patient administered with the said capsule for a long time.

The third essential component of the composition according to the present invention is oil. Oil that can be used in the composition of the present invention comprises vegetable oils; esterification products of vegetable oils; animal oils and derivatives thereof; and unsaturated long chain fatty acids. They may be used alone or as the mixture of two kinds or more. In case of mixture, the selection may be performed only in one small group of the said classification; or in two or more small groups of the said classification.

Examples of vegetable oils that can be used in the composition of the present invention are corn oil, borage oil, sesame oil, primrose oil, peanut oil, olive oil, etc. Refined vegetable oils are preferred.

The refined vegetable oils have the high purity and low contents of impurities, and can be controlled the contents of unsaturated long chain fatty acids. Therefore, they have been used mainly in the total parenteral nutrition, for the wasting disease such as diabetic nervous disease, rheumatic arthritis, etc., and as vehicle for stabilization of unstable drug. The refined vegetable oils, which passed through refining procedure by chromatography, are more transparent than general oils. Because oxidants such as aldehydes, alcohols, ketones, etc. are removed from them, they are more resistant to oxidation than general oils. And because the polar materials and water contents of them are reduced highly, they have more excellent solubilization effect for drug than general oils. The commercial refined vegetable oils generally have peroxide value of 0.5 or less than, anisidine value of 0.2~0.5, and acid value of 0.1~1.0 or less. The commercial refined vegetable oils have various contents of unsaturated fatty acids depending on the kind of vegetable oil. The oil having the proper content of unsaturated fatty acids for the requirement, therefore, may be selected and used.

Examples of the refined vegetable oils, which are preferable oils of the composition according to the present invention, are super-refined corn oil, borage oil, sesame oil, primrose oil, peanut oil and olive oil, which are on the market as trade name Super-refined oil (Croda Co.). The more preferable oil that can be used in the composition according to the present invention is the form that the content of high gamma linolenic acid in the oil is increased in more than 50 %. Example of that oil is concentrated borage oil of trade name Crossential (Croda Co.).

As another oil component that can be used in the composition

according to the present invention, esterification products of vegetable oils comprise i) the product from esterification of vegetable oil with glycerin; ii) the product from esterification of vegetable oil with monohydric alcohol; iii) the product from esterification of vegetable oil with triacetin; and iv) the product from esterification of vegetable oil with polyglycerol. The said esterification of vegetable oil means that fatty acids contained in vegetable oils undergo the esterification reaction. The esterification products, a mixture of various components, may be separated and refined to form a pure objected material. And then, this pure material may be used as an oil component in the composition of the present invention. Moreover, the fatty acids contained in vegetable oils may be separated and refined, and then may be esterification-reacted to form the said products separately.

In the esterification products of vegetable oils, at first, the product from esterification of vegetable oil with glycerin may be used. The product comprises fatty acid triglycerides; mono-glycerides; mono- and di-glycerides; or a mixture of two thereof .

As a class of the product from esterification of vegetable oil with glycerin, fatty acid triglycerides may be used. C_8~C_{12} fatty acid medium chain triglyceride (MCT) is preferable fatty acid triglycerides. MCT is prepared by esterification of fatty acids extracted from palm oil with glycerin, and is triglyceride of medium chain fatty acids of which main fatty acids are capric acid (50~80 %) and caprylic acid (20~50 %). Compared to general vegetable oils, MCT provides many advantages. Since MCT is more stable against oxidation and higher density as close value (0.94~0.95) to the density of water than general oil, an emulsion using the said medium chain fatty acid is more stable than general emulsions. In addition, due to MCT is less hydrophobic than vegetable oils,

it is possible to obtain a higher concentration of the active ingredient without a significant increase in the viscosity of the composition when the composition of the present invention is prepared using MCT. This means that MCT is an oil very suitable to the drug of which the dose is great such that the concentration of active ingredient to carrier is as high as 10% and which has very low polarity and therefore, is very slightly soluble in water, for example, cyclosporin. MCT has been commercialized under the trade names Sefol 860, Sefol 870, Sefol 880, Miglyol 810, Miglyol 812, Miglyol 818, Labrafac CC, etc.

As another class of the product from esterification of vegetable oil with glycerin, mono- and di- glycerides may be used. The name of 'mono- and di- glycerides' means the form of a mixture of glycerol mono- and di- esters of a fatty acid. Mono- and di- glycerides is an oil which is obtained through esterification of fatty acids contained in vegetable oil with glycerin followed by separation and refining, and has many kinds depending on the kind of fatty acid and the extent of esterification. Mono- and di- glycerides that the ratio of monoglyceride to total glycerides is at least 40 %, preferably at least 90 % and of which fatty acid is high chain of C_{16}~C_{18} may be used preferably. It is more preferable that mono- and di- glycerides contain a monoglyceride of C_{18} fatty acid as its main component. Such a compound has been commercialized under the trade name GMO AV1 (Croda Co.), ATMOS 300 (ICI Co.), GMOrphic-80 (Eastman Co.), etc. Especially, GMOrphic-80 is a pure monoglyceride that does not have diglyceride, because it is prepared through isolation of only monoglyceride using molecular distillation following after esterification. Accordingly, GMOrphic-80 is an example of more and more preferable oil component in the composition according to the present invention.

In the esterification products of vegetable oils, at second, the product from esterification of vegetable oils with monohydric alcohol may be used. There are many kinds of the said product according to the kinds of vegetable oil reacted. The representative example comprises Crossential GLO E50 (concentrated borage oil ethyl ester; Croda Co.), which is the product from esterification of borage oil with ethanol, and Nikkol E00 (ethyl olive oleate; Nikkol Co.), which is the product from esterification of olive oil with ethanol. The said product may be also prepared using only fatty acid component isolated from vegetable oil instead of using total 'vegetable oil' components. Examples of this product include ethyl oleate, ethyl linoleate, isopropyl palmitate, isopropyl myristate, etc.

In the esterification products of vegetable oils, at third, the product from esterification of vegetable oils with triacetin may be used. Examples of the said product comprise mono- and di- acetylated monoglycerides; and di-acetylated monoglyceride. Diacetylated monoglyceride of C_{14}~C_{20} fatty acid is preferred. The said diacetylated monoglyceride is the product from esterification of edible oils with triacetin. The said diacetylated monoglyceride is used as additive in foods and as plasticizer in medicines, and has been commercialized under the trade name Mivacet 9-40, Mivacet 9-45, etc. The said product may be obtained from esterification of triglycerides with triacetin.

In the esterification products of vegetable oils, at fourth, the product from esterification of fatty acid with polyglycerol, that is, polyglyceryl fatty acid ester, may be used. Examples of polyglycerol used in esterification include diglycerol, tetraglycerol, hexaglycerol, decaglycerol, decaglycerol, etc. Examples of fatty acid reacted with those polyglycerol include oleic acid, linoleic acid, stearic acid, etc. Examples of

polyglyceryl fatty acid ester include Plurol Oleique CC 497 (polyglyceryl oleate; Gattefosse Co.), Plurol Stearique (polyglyceryl palmitostearate; Gattefosse Co.), DGMO-C (diglyceryl monooleate; Nikkol Co.), Tetraglyn 1-0 (tetraglyceryl monooleate; Nikkol Co.), Hexaglyn 1-0 (hexaglyceryl monooleate; Nikkol Co.), Hexaglyn 5-0 (hexaglyceryl pentaoleate; Nikkol Co.), Decaglyn 5-0 (Decaglyceryl pentaoleate; Nikkol Co.), Decaglyn 10-0 (Decaglyceryl decaoleate; Nikkol Co.), etc.

Moreover, animal oils and derivatives thereof may be used as an oil component in the composition according to the present invention. The first example of animal oils and derivatives thereof is squalenes. Squalene, which is obtained from the liver oil of shark, is colorless and transparent oil and its chemical name is hexamethyltetracosa-hexaene. Compared to general animal oils, squalene is more excellent in the stability against oxidation, and has lower melting point. Therefore, it could dissolve cyclosporin effectively. Hydrogenated squalene may be also used as oil component in the cyclosporin-containing microemulsion preconcentrate composition. Examples of squalenes commercial products include Squalene EX (Nikkol Co.), Squalene (Nikkol Co.), etc.

The second example of animal oils and derivatives thereof comprises omega-3 essential fatty acids, an oil of ethyl esterificated form of the said fatty acids and an oil of triglyceride form of the said fatty acids. 'Omega-3 essential fatty acids' is an animal oil of which fatty acid component is eicosapentaenoic acid and docosahexaenoic acid. Examples of commercial product of 'omega-3 essential fatty acids' include Incromega F2250 (Croda Co.) and Incromega F2628 (Croda Co.). Examples of commercial product of ethyl esterificated form of the said

fatty acids include Incromega E2251 (Croda Co.), Incromega F2573 (Croda Co.), etc. Examples of commercial product of triglyceride form of the said fatty acids include Incromega TG2162 (Croda Co.), Incromega TG2779 (Croda Co.), Incromega TG2928 (Croda Co.), etc.

Moreover, unsaturated long chain fatty acids may be used as an oil component in the composition according to the present invention. Examples of such fatty acids include oleic acid, linoleic acid, linolenic acid, etc. There are examples of their commercial products such as

Crossential 094 (Croda Co.), which is the commercial product of oleic acid;

Crossential L99 (Croda Co.), which is the commercial product of linoleic acid; and

Crossential LN80 (Croda Co.), which is the commercial product of linolenic acid.

The said various oils may be used with combinations of proper ratio to control cyclosporin absorption.

In the cyclosporin-containing microemulsion preconcentrate composition according to the present invention, the ratio of oil component to cyclosporin is preferably in the range of 1:0.1~5, more preferably 1:1~3 by weight.

The fourth essential component of the composition according to the present invention is a surfactant. Any pharmaceutical acceptable surfactant may be used, provided it is miscible with both the oil and the lipophilic solvent components to form an emulsion under mild stirring in the external

phase and can adjust the particle diameter in the inner phase to 100 nm or below by controlling the constitutional ratio thereof. Surfactants which may be used for this purpose have preferably HLB value of 1~20, and there are examples of them as following:

i) Reaction products of natural or hydrogenated vegetable oils and ethylene glycol; i. e., polyoxyethylene glycolated natural or hydrogenated vegetable oils: for example polyoxyethylene glycolated natural or hydrogenated castor oils. Surfactants commercialized under the trade names Cremophor RH40, Cremophor RH60, Cremophor EL, Nikkol HCO-40 and Nikkol HCO-60 may be used in the composition according to the present invention. Cremophor RH40 and Cremophor EL are preferred.

ii) Polyoxyethylene sorbitan fatty acid esters: e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g. products of the trade name "Tween", which includes polyoxyethylene (20) sorbitan mono-laurate (Tween 20), polyoxyethylene (20) sorbitan mono-palmitate (Tween 40), polyoxyethylene (20) sorbitan mono-oleate (Tween 80), etc. depending on the kind of fatty acid. Tween 20 and Tween 40 can be used preferably in the composition according to the present invention.

iii) Polyoxyethylene fatty acid esters: for example, polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj as well as polyoxyethylene fatty acid esters known and commercially available under the trade name "Cetiol HE".

iv) Polyoxyethylene-polyoxypropylene co-polymers: e.g. of the type known and commercially available under the trade names "Pluronic" and "Emkalyx".

v) Polyoxyethylene-polyoxypropylene block co-polymers: e.g. of the type

known and commercially available under the trade name "Poloxamer".

vi) Dioctylsuccinate, dioctylsodiumsulfosuccinate, di-[2 - ethylhexyl]-succinate or sodium lauryl sulfate.

vii) Phospholipids, in particular lecithins: especially, soybean lecithin.

viii) Bile salts: e.g. alkali metal salts, for example sodium taurocholate.

ix) Trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; e.g. of the type known and commercially available under the trade name Labrafil. Specially, Labrafil M 1944 CS, Labrafil WL 2609 BS, Labrasol, etc. can be used preferably in the composition according to the present invention.

x) Mono-, di-and mono/di-glycerides: especially esterification products of caprylic or capric acid with glycerol.

xi) Sorbitan fatty acid esters: for example, of the type known and commercially available under the trade name Span.

xii) Pentaerythritol fatty acid esters and polyalkylene glycol ethers, for example pentaerythrite -dioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as pentacrythrite-fatty acid esters.

xiii) Sterols and derivatives thereof, for example cholesterols and derivatives thereof, in particular phytosterols: e.g. products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof, such as known under the trade name Generol.

xiv) Polyethylene glycol 660 12-hydroxystearate: for example, of the type known and commercially available under the trade name Solutol HS 15.

xv) Polyethylene glycol fatty acid esters: according to the kind of fatty acid attached, it may be classified in –stearate, –laurate, –oleate, etc. Polyethylene glycol monooleate is preferable, and examples of its

commercial product are MYO-2, MYO-6, MYO-10, etc.

xvi) Di- α -tocopheryl polyethylene glycol 1000 succinate

Surfactants that may be used more preferably in the composition according to the present invention are polyoxyethylene glycolated natural or hydrogenated vegetable oils; polyoxyethylene sorbitan fatty acid esters; trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; and polyethylene glycol fatty acid esters.

The said surfactants can be used alone or in the mixture of two kinds or more. In the cyclosporin-containing microemulsion preconcentrate composition according to the present invention, the ratio of oil component to cyclosporin is preferably in the range of 1:2~10, more preferably 1:3~8 by weight.

In the cyclosporin-containing microemulsion preconcentrate composition according to the present invention, the said four essential components should be present preferably in the mixing ratio of cyclosporin: lipophilic solvent: surfactant: oil =1 : 0.1~5 : 2~10 : 0.1~5, and more preferably in the mixing ratio of cyclosporin: lipophilic solvent: surfactant: oil =1 : 1~3 : 3~8 : 1~3, on the basis of weight.

The composition according to the present invention is characterized in that it dissolves in an external phase such as water, artificial gastric fluid and artificial intestinal fluid by controlling the mixing ratio of the components thereby to get the microemulsion form of inner phase diameter of 100 nm or below.

The cyclosporin-containing composition according to the present invention may further comprise any pharmaceutically acceptable additives

as needed. Examples of the said additives include antioxidant (e.g., tocopherol, butylated hydroxyanisole (BHA), etc.), viscosity control agent, dissolution control agent, flavor (e.g., peppermint oil, etc.), preservatives (e.g., benzyl alcohol, parabens, etc.) and coloring agents.

For clinical use, the composition according to the present invention can be formulated as the dosage form of a soft capsule, a hard capsule sealed with a gelatin banding at the conjugated portion, or an oral liquid preparation to administer into patient orally. The composition of the present invention can be formulated into soft capsules by the conventional method, for example, by dissolving cyclosporin in lipophilic solvent component under mild warming, adding the oil and surfactant components to the resulting solution, uniformly mixing the constituents, then, if necessary, adding pharmaceutically acceptable additives, and finally formulating the resulting mixture, i.e. the composition according to the present invention, into soft capsules using a machine for preparing soft capsule.

Microemulsion preconcentrate prepared with lipophilic solvent instead of hydrophilic solvent according to the present invention, especially used as the dosage form of soft capsule, yields higher blood concentration of cyclosporin than commercial product of cyclosporin soft capsule, and the resultant capsule do not exhibit any change of composition with time due to volatilization and permeation of the components. Moreover, it reduces the manufacturing cost and the toxicity of solvent, which may make a problem in long-term therapy. The cyclosporin-containing composition according to the present invention, therefore, represents and improves over cyclosporin soft capsules of the prior art.

BRIEF DESCRIPTION OF THE DRAWINGS

For a thorough understanding of the nature and objects of the invention, reference should be had to the following detailed description taken in connection with the accompanying drawings in which:

Figure 1 shows blood concentration-time profiles of cyclosporin following the oral administration of cyclosporin commercial product (Sandimmun®: comparative preparation) and cyclosporin-containing microemulsion preconcentrate compositions according to the present invention (test preparations) to dogs (◆-◆, comparative preparation; □-□, test preparation 6-A; △-△, test preparation 7-B; ■-■, test preparation 8-C; ▲-▲, test preparation 9-D).

MODES FOR CARRING OUT THE INVENTION

The present invention is described in more detail by Examples and Experiment as shown below but is not confined to the said scopes.

Example 1. Cyclosporin soft capsule for oral administration

The soft capsule containing the composition of 1-A in Table 1 according to the present invention was prepared as following procedure:

50 g of cyclosporin A as an active ingredient was dissolved in 150 g of triethyl citrate as a lipophilic solvent component with stirring and heating. 125 g of Miglyol 812 as an oil component and 225 g of Cremophor RH 40 as a surfactant component were added to obtain the mixture, which was stirred until a homogeneous solution was formed. The resulting composition was poured to a machine for preparing soft capsules and then encapsulated according to conventional methods for producing

soft capsules. Each capsules contained 50 mg of cyclosporin A.

The soft capsule preparations of Examples 1-B to 1-D, having the compositions given in the following Table 1, were also prepared according to the said method.

Table 1

Components		Composition (mg/capsule)			
		Example 1-A	Example 1-B	Example 1-C	Example 1-D
Active ingredient	Cyclosporin A	50.0	50.0	50.0	50.0
Lipophilic solvent	Triethyl citrate	150.0			50.0
	Triacetin		125.0		
	Acetyltriethyl citrate			150.0	100.0
Surfactant	Cremophor RH 40	225.0	175.0	180.0	90.0
	Tween 20		75.0	50.0	150.0
Oil	Miglyol 812	125.0	125.0	110.0	110.0
Total		550.0	550.0	540.0	550.0

Example 2. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 2-A to 2-F, having the compositions given in the following Table 2, were prepared according to the method of Example 1.

Table 2

Components		Composition (mg/capsule)					
		Example 2-A	Example 2-B	Example 2-C	Example 2-D	Example 2-E	Example 2-F
Active ingredient	Cyclosporin A	50.0	50.0	50.0	50.0	50.0	50.0
Lipophilic solvent	Triethyl citrate	120.0		80.0		40.0	
	Triacetin		140.0			40.0	50.0
	Tributyl citrate						40.0
	Acetyltri-butyl citrate			40.0			
	Acetyltriethyl citrate	20.0	10.0		80.0		
Surfactant	Cremophor RH 60	200.0	210.0	220.0	150.0	70.0	
	Tween 20		20.0		70.0	150.0	220.0
Oil	GMOrphic 80	50.0	80.0		130.0	30.0	30.0
	DGMO-C	100.0		50.0		50.0	
	Mivacet 9-45		70.0	80.0		50.0	100.0
Total		540.0	580.0	520.0	480.0	480.0	490.0

Example 3. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 3-A to 3-F, having the compositions given in the following Table 3, were prepared according to the method of Example 1.

Table 3

Components		Composition (mg/capsule)					
		Example 3-A	Example 3-B	Example 3-C	Example 3-D	Example 3-E	Example 3-F
Active ingredient	Cyclosporin A	50.0	50.0	50.0	50.0	50.0	50.0
Lipophilic solvent	Triethyl citrate	80.0		80.0			
	Triacetin		110.0				
	Tributyl citrate	30.0	20.0		120.0		
	Acetyltri-butyl citrate	10.0		40.0		100.0	
	Acetyltriethyl citrate	20.0	10.0				150.0
Surfactant	Cremophor EL	150.0	210.0	220.0		70.0	
	Tween 20		20.0		150.0	150.0	
	MYO-2	60.0	30.0		30.0	30.0	180.0
	Labrafil	50.0		50.0		50.0	
Oil	Super-refined borage oil	150.0	100.0	120.0	130.0	100.0	130.0
Total		600.0	550.0	560.0	480.0	550.0	510.0

Example 4. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 4-A to 4-F, having the compositions given in the following Table 4, were prepared according to the method of Example 1.

Table 4

Components		Composition (mg/capsule)					
		Example 4-A	Example 4-B	Example 4-C	Example 4-D	Example 4-E	Example 4-F
Active ingredient	Cyclosporin A	50.0	50.0	50.0	50.0	50.0	50.0
Lipophilic solvent	Triacetin	80.0		120.0		50.0	
	Acetyltri-butyl citrate		130.0			20.0	100.0
	Acetyltriethyl citrate		20.0		130.0	30.0	
Surfactant	Cremophor RH 40	200.0	210.0	220.0	180.0	250.0	200.0
Oil	Miglyol 812		90.0				
	Plurol oleique CC 497		40.0	70.0	100.0	20.0	
	GMOrphic 80	70.0			10.0		
	Super-refined olive oil			10.0		30.0	
	Linolenic acid					40.0	
	Crossential GLO E50			60.0	30.0		150.0
	Ethyl linoleate	80.0				50.0	
Total		480.0	540.0	530.0	500.0	540.0	500.0

Example 5. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 5-A to 5-E, having the compositions given in the following Table 5, were prepared according to the method of Example 1.

Table 5

Components		Composition (mg/capsule)				
		Example 5-A	Example 5-B	Example 5-C	Example 5-D	Example 5-E
Active ingredient	Cyclosporin A	50.0	50.0	50.0	50.0	50.0
Lipophilic solvent	Triethyl citrate	100.0		80.0		90.0
	Acetyltriethyl citrate	30.0	120.0		120.0	
Surfactant	Cremophor RH 40	180.0	210.0	220.0	220.0	250.0
Oil	Tetraglyn 1-0	100.0	80.0	80.0		
	Mivacet 9-40		20.0		110.0	
	GMOrphic 80	10.0	30.0		20.0	50.0
	Ethyl oleate			40.0		
	Ethyl linoleate	30.0		30.0	10.0	80.0
Antioxi-dant	Tocopherol	0.7	1.0	3.0	1.5	2.0
Total		500.7	511.0	503.0	531.5	522.0

Example 6. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 6-A to 6-D, having the compositions given in the following Table 6, were prepared according to the method of Example 1. These soft capsules contain 100 mg of cyclosporin A per capsule.

Table 6

Components		Composition (mg/capsule)			
		Example 6-A	Example 6-B	Example 6-C	Example 6-D
Active ingredient	Cyclosporin A	100.0	100.0	100.0	100.0
Lipophilic solvent	Triethyl citrate	50.0			150.0
	Triacetin	100.0	250.0	150.0	20.0
	Tributyl citrate			50.0	20.0
Surfactant	Cremophor RH 40	450.0	300.0	200.0	450.0
	Tween 20		150.0	200.0	
Oil	GMOrphic 80	80.0			
	DGMO-C	220.0			230.0
	Tetraglyn 1-0		50.0	150.0	
	Sefol 880		150.0		50.0
	Super-refined borage oil		50.0	150.0	
Total		1000.0	1050.0	1000.0	1020.0

Example 7. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 7-A to 7-D, having the compositions given in the following Table 7, were prepared according to the method of Example 1. These soft capsules contain 100 mg of cyclosporin A per capsule.

Table 7

Components		Composition (mg/capsule)			
		Example 7-A	Example 7-B	Example 7-C	Example 7-D
Active ingredient	Cyclosporin A	100.0	100.0	100.0	100.0
Lipophilic solvent	Triethyl citrate	180.0			150.0
	Triacetin		250.0	200.0	40.0
Surfactant	Cremophor RH 40	350.0	300.0	200.0	450.0
	Tween 20		150.0	200.0	
Oil	Plurol oleique CC 497	100.0		50.0	150.0
	Tetraglyn 1-0	80.0	50.0		
	GMOrphic 80			50.0	
	Nikkol E00	120.0	150.0		
	Crossential GLO E50		100.0	150.0	150.0
Total		930.0	1100.0	950.0	1040.0

Example 8. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 8-A to 8-D, having the compositions given in the following Table 8, were prepared according to the method of Example 1. These soft capsules contain 100 mg of cyclosporin A per capsule.

Table 8

Components		Composition (mg/capsule)			
		Example 8-A	Example 8-B	Example 8-C	Example 8-D
Active ingredient	Cyclosporin A	100.0	100.0	100.0	100.0
Lipophilic solvent	Triethyl citrate	100.0			150.0
	Triacetin	100.0	250.0	200.0	40.0
Surfactant	Cremophor RH 40	380.0	300.0	200.0	420.0
	Tween 80		150.0	200.0	
Oil	Plurol oleique CC 497	100.0		120.0	50.0
	GMOrphic 80	100.0	50.0		
	Incromega F2250	100.0			70.0
	Incromega E2251		150.0		
	Incromega TG2779			150.0	80.0
Total		980.0	1000.0	970.0	910.0

Example 9. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 9-A to 9-D, having the compositions given in the following Table 9, were prepared according to the method of Example 1. These soft capsules contain 100 mg of cyclosporin A per capsule.

Table 9

Components		Composition (mg/capsule)			
		Example 9-A	Example 9-B	Example 9-C	Example 9-D
Active ingredient	Cyclosporin A	100.0	100.0	100.0	100.0
Lipophilic solvent	Triethyl citrate	150.0		100.0	
	Triacetin	50.0	250.0	100.0	210.0
Surfactant	Cremophor RH 40	400.0	300.0	100.0	430.0
	Tween 20		150.0	300.0	70.0
	Cremophor EL				70.0
	Poloxamer 124				70.0
Oil	Plurol oleique CC 497	70.0		120.0	
	GMOrphic 80	80.0	50.0		
	Decaglyn 5-0	150.0			
	Oleic acid		150.0	50.0	
	Linoleic acid				115.0
	Labrafac CC			50.0	285.0
Total		1000.0	1000.0	920.0	1350.0

Example 10. Cyclosporin soft capsule for oral administration

The soft capsule preparations of Examples 10-A to 10-D, having the compositions given in the following Table 10, were prepared according to the method of Example 1. These soft capsules contain 100 mg of cyclosporin A per capsule.

Table 10

Components		Composition (mg/capsule)			
		Example 10-A	Example 10-B	Example 10-C	Example 10-D
Active ingredient	Cyclosporin A	100.0	100.0	100.0	100.0
Lipophilic solvent	Triethyl citrate	100.0			50.0
	Triacetin	100.0	200.0	200.0	100.0
Surfactant	Cremophor RH 40	350.0	200.0	100.0	450.0
	Tween 80		180.0	300.0	
Oil	Plurol oleique CC 497	50.0		50.0	
	GMOrphic 80	50.0	150.0		
	Tetraglyn 5-0	200.0			
	Squalene EX		150.0	200.0	
	Squalene				200.0
Total		950.0	980.0	950.0	900.0

Example 11~20. Cyclosporin hard capsule for oral administration

The cyclosporin-containing microemulsion preconcentrate compositions were prepared in the same compositions and methods with Examples 1 to 10, and then were filled in hard gelatin capsules. The

conjugated portion of the hard capsules was sealed with gelatin banding to produce hard capsules containing 50 or 100 mg of cyclosporin A per capsule.

Experimental example 1.

To compare the pharmacological effect of the cyclosporin-containing microemulsion preconcentrate composition according to the present invention with that of commercial product prepared according to prior art, the bioavailability comparison experiment was performed using dogs as follows. The soft capsules of Examples 6-A, 7-B, 8-C and 9-D were used as test preparations according to the present invention, and Sandimmun® 100-mg soft capsules, which are commercial product, were used as a comparative preparation.

In this bioavailability study, fifteen male dogs, weighing 11.0~15.0 kg, were used, and each groups was consisted with three dogs. No food except water was supplied to dogs for 18 h prior to drug administration. The dogs were given each soft capsules preparations with the dose of cyclosporin A 100 mg per a dog, and then 50 ml of water was administered immediately. After 4 h from drug administration, food was provided. Venous blood samples of 2 ml was withdrawn in the cephalic vein before drug administration for baseline cyclosporin A levels, and at schedule time intervals after dosing. Blood samples were frozen under -18°C until assay. Blood concentrations of cyclosporin A were analyzed by RIA (radioimmunoassay) method.

The dog whole blood cyclosporin A concentration *vs.* time curves of each preparations are presented in Fig. 1, and the pharmacokinetic parameters calculated from the experimental data are given in the

following Table 11.

Table 11. Bioavailability of the test preparation of the present invention and the comparative preparation

Pharmacokinetic parameters	Test preparations				Comparative preparation
	Example 6-A	Example 7-B	Example 8-C	Example 9-D	
AUC_{0-24} (ng ·h/ml)	5910.4	4887.7	4807.4	6121.7	2671.4
C_{max} (ng/ml)	1224.3	987.26	1026.3	1118.0	512.0
T_{max} (h)	1.5	1.5	2.0	2.0	2.0

As can be shown from Fig. 1 and Table 11, the cyclosporin-containing microemulsion preconcentrate compositions using lipophilic solvent according to the present invention showed very larger AUC (area under the curve of cyclosporin A blood concentration) as well as higher C_{max} (maximum blood concentration of cyclosporin A) than comparative preparation did. Compared with comparative preparation, the AUC of cyclosporin A after the oral administration of test preparation 6-A, 7-B, 8-C and 9-D were 2.21, 1.83, 1.80 and 2.29 times, respectively, and, that is, the test preparations showed high absorption pattern.

From the results of Experimental example as mentioned above, it was certified that the composition of the present invention has high bioavailability of two or more times compared with preparation of prior art, and may show the excellent effect of cyclosporin. In addition, the cyclosporin-containing microemulsion preconcentrate composition according to the present invention provide the excellent cyclosporin preparation which can overcome the various disadvantages, that is,

forming of cyclosporin precipitation due to solvent evaporation, non-expectable changing of cyclosporin bioavailability induced from drug precipitating, undesirable changing of preparation external appearance, increasing of production cost due to use of special package, etc.

CLAIMS

1. A cyclosporin-containing microemulsion preconcentrate composition which comprises:

1) a cyclosporin as an active ingredient;
2) an alkyl ester of polycarboxylic acid and/or a carboxylic acid ester of polyols as a lipophilic solvent;
3) an oil; and
4) a surfactant.

2. A composition according to claim 1, wherein the said cyclosporin is cyclosporin A.

3. A composition according to claim 1, wherein the said alkyl ester of polycarboxylic acid is at least one member selected from the group consisting of triethyl citrate, tributyl citrate, acetyltributyl citrate, and acetyltriethyl citrate.

4. A composition according to claim 1, wherein the said carboxylic acid ester of polyols is triacetin.

5. A composition according to claim 1, wherein the said oil is at least one member selected from the group consisting of a vegetable oil; an esterification product of vegetable oil; an animal oil and derivative thereof; and an unsaturated long chain fatty acid.

6. A composition according to claim 5, wherein the said vegetable oil is a

refined vegetable oil.

7. A composition according to claim 6, wherein the said refined vegetable oil is at least one member selected from Super-refined forms of corn oil, borage oil, sesame oil, primrose oil, peanut oil and olive oil.

8. A composition according to claim 5, wherein the said esterification product of vegetable oil is

i) a product from esterification of vegetable oil with glycerin;

ii) a product from esterification of vegetable oil with monohydric alcohol;

iii) a product from esterification of vegetable oil with triacetin; and

iv) a product from esterification of vegetable oil with polyglycerol.

9. A composition according to claim 8, wherein the said product from esterification of vegetable oil with glycerin is fatty acid triglycerides; mono-glycerides; mono- and di- glycerides; or a mixture of two thereof.

10. A composition according to claim 9, wherein the said fatty acid triglyceride is C_8~C_{12} fatty acid medium chain triglyceride.

11. A composition according to claim 9, wherein the said mono- and di-glycerides is C_{16}~C_{18} fatty acid mono- and di- glycerides

12. A composition according to claim 8, wherein the said product from esterification of vegetable oil with monohydric alcohol is a product from esterification of borage oil or olive oil with monohydric alcohol.

13. A composition according to claim 8, wherein the said product from esterification of vegetable oil with monohydric alcohol is at least one member selected from the group consisting of ethyl oleate, ethyl linoleate, isopropyl palmitate and isopropyl myristate.

14. A composition according to claim 8, wherein the said product from esterification of vegetable oil with triacetin is C_{14}~C_{20} fatty acid mono- and di-acetylated monoglyceride.

15. A composition according to claim 8, wherein the said product from esterification of vegetable oil with polyglycerol is an oil formed from esterification of fatty acid with di-, tetra-, hexa- or deca-glycerol.

16. A composition according to claim 5, wherein the said animal oil and derivative thereof is at least one component selected from the group consisting of squalenes; omega-3 essential fatty acid; oils formed from the esterification of omega-3 essential fatty acid with monohydric alcohol; and oils of triglyceride form of omega-3 essential fatty acid.

17. A composition according to claim 1, wherein the said surfactant has HLB value of 1~20.

18. A composition according to claim 17, wherein the said surfactant is at least one member selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene fatty acid esters;

polyoxyethylene-polyoxypropylene co-polymers; polyoxyethylene-polyoxypropylene block co-polymers; dioctylsuccinate, dioctyl sodium sulfosuccinate, di-[2-ethylhexyl]-succinate or sodium lauryl sulfate; phospholipids; bile salts; trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; mono-, di- and mono/di-glycerides; sorbitan fatty acid esters; pentaerythritol fatty acid esters and polyalkylene glycol ethers, and pentaerythrite fatty acid esters; sterols and derivatives thereof; polyethylene glycol 660 12-hydroxystearate; polyethylene glycol fatty acid esters; and di-α-tocopheryl polyethylene glycol 1000 succinate.

19. A composition according to claim 18, wherein the said surfactant is at least one member selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils; polyoxyethylene sorbitan fatty acid esters; trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; and polyethylene glycol fatty acid esters.

20. A composition according to claim 19, wherein the said surfactant is at least one member selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils; and polyoxyethylene sorbitan fatty acid esters.

21. A composition according to claim 1, wherein the said cyclosporin, the said lipophilic solvent, the said surfactant and the said oil component is present in the mixing ratio of 1 : 0.1~5 : 2~10 : 0.1~5 on the basis of weight.

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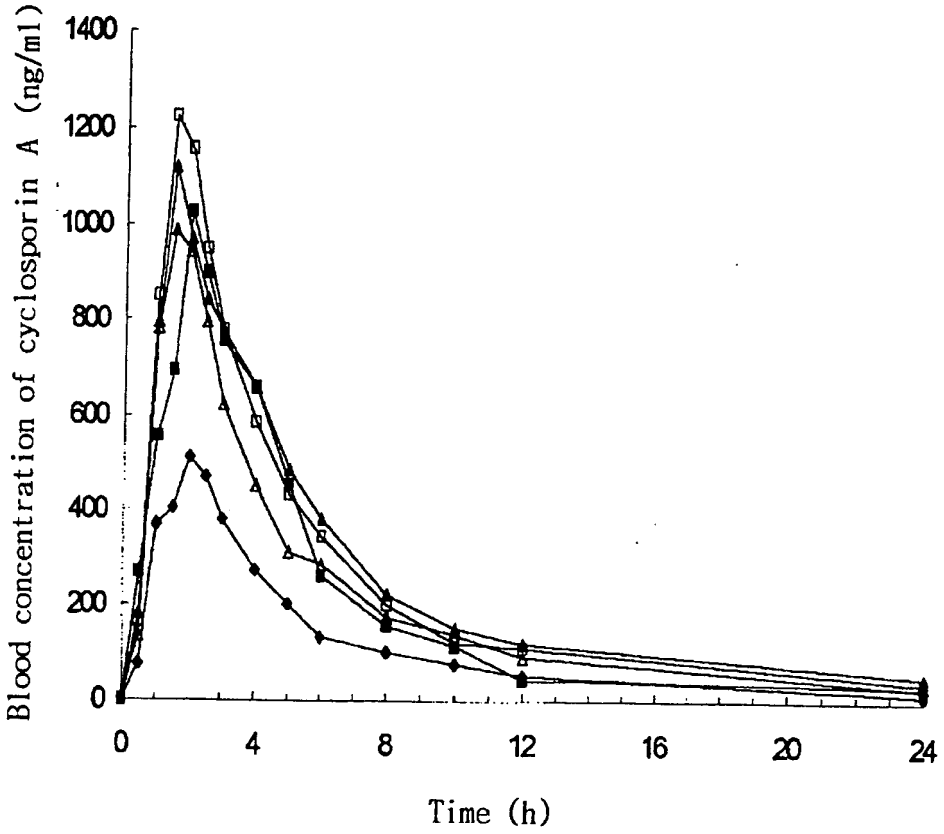
22. A composition according to claim 21, wherein the said cyclosporin, the said lipophilic solvent, the said surfactant and the said oil component is present in the mixing ratio of 1 : 1~3 : 3~8 : 1~3 on the basis of weight.

23. A composition according to claim 1, wherein it further comprises at least one species of pharmaceutically acceptable additives selected from the group consisting of antioxidant, viscosity control agent, dissolution control agent, flavor, preservatives and coloring agents.

24. A pharmaceutical formulation comprising the composition according to claims 1, wherein the dosage form is a soft capsule, a hard capsule sealed with a gelatin banding at the conjugated portion, or an oral liquid preparation.

FIG. 1


Blood concentration of cyclosporin A (ng/ml)
1400
1200
1000
800
600
400
200
0
0
4
8
12
16
20
24
Time (h)

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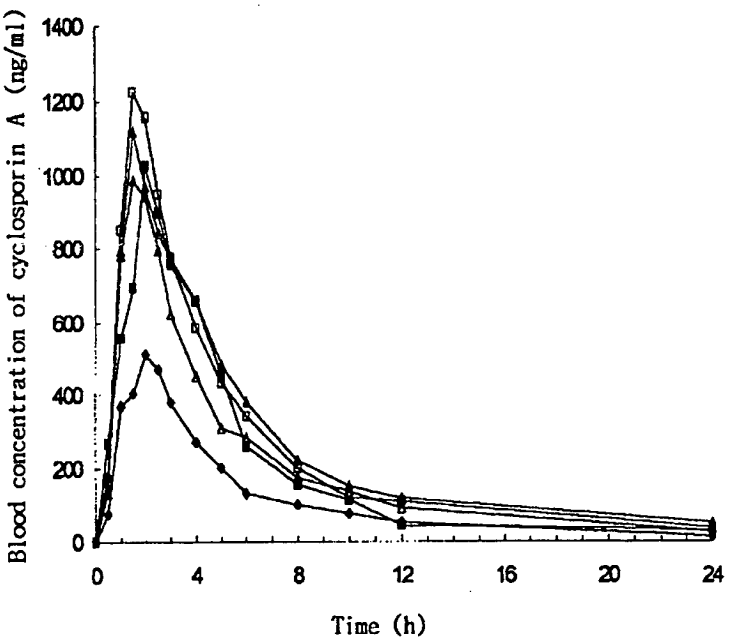
(54) Title: CYCLOSPORIN-CONTAINING MICROEMULSION PRECONCENTRATE COMPOSITION

(57) Abstract

The present invention relates to a microemulsion preconcentrate composition comprising (1) cyclosporin as an active component; (2) alkyl ester of polycarboxylic acid and/or carboxylic acid ester of polyols as a lipophilic solvent; (3) oil; and (4) surfactant. The composition according to the present invention is characterized in that it dissolves in an external phase such as water, artificial gastric fluid and artificial intestinal fluid by controlling the mixing ratio of the components thereby to get the microemulsion form of inner phase diameter of 100 nm or below. The composition according to the present invention can be formulated as the dosage form of a soft capsule, a hard capsule sealed with a gelatin banding at the conjugated portion, or an oral liquid preparation for oral administration. Especially, in the case that the composition according to the present invention is formulated in a soft capsule, the resultant capsule does not show the disadvantages of the prior arts such as the reactivity of hydrophilic solvent with gelatin shell of soft capsule and the volatility of hydrophilic solvent. It is because the existing patents use a hydrophilic solvent as an essential component of their compositions but the present invention does not use any hydrophilic solvent.



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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Name and mailing address of the ISA/	Authorized officer
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